

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761128Orig1s000

PRODUCT QUALITY REVIEW(S)



**U.S. FOOD & DRUG
ADMINISTRATION**

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	November 12, 2019
Assessor:	Scott Dallas, RPh, Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Mekonnen LemmaDechassa, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research III
Application:	BLA 761128
Applicant:	Novartis Pharmaceuticals Corporation
Submission Dates:	February 19, March 15, April 30, July 9, October 16, November 1 and November 12, 2019
Product:	Adakveo (crizanlizumab-tmca)
Dosage form(s):	Injection
Strength and Container-Closure:	100 mg/10 mL (10 mg/mL)
Purpose of assessment:	The Applicant submitted a biologics license application seeking approval of a new indication in the treatment of sickle cell disease.
Recommendations:	The prescribing information, patient labeling, container labels, and carton labeling are acceptable from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	Appendix Section
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

(b) (4)

CONCLUSION

The prescribing information and patient labeling submitted on November 12, 2019 and the container labels, and carton labeling submitted on November 1, 2019 were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES**Appendix A:** Proposed Labeling

- Prescribing Information and Patient Information (submitted on April 30, 2019)
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- Container Labels (submitted on March 15, 2019)

(b) (4)

- Carton Labeling (submitted on March 15, 2019)

(b) (4)

Appendix B: Evaluation Tables

Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Proper Name	Acceptable
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<i>Recommended labeling practices (placement of dosage form below the proper name)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
To Applicant: Consider including the dosage formulation, "injection", directly beneath the proper name on the principal display panel.	
October 16, 2019: The applicant included the dosage formulation, "injection", directly beneath the proper name on the principal display panel.	
FDA Response: The applicant's revision is acceptable.	
Manufacturer name, address, and license number	Acceptable
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
To Applicant: Revise the manufactured by name "Novartis" to read "Novartis Pharmaceuticals Corporation" per 21 CFR 610.60(c) and 21 CFR 600.3(t). Also note if the only manufacturer information on the label is the licensed manufacturer, then "Manufactured by" or "Mfg by:" may be omitted.	
October 16, 2019: The applicant included the complete manufacturer's name, Novartis Pharmaceuticals Corporation.	
FDA Response: The applicant's revision is acceptable.	
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per 21 CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

	☐ N/A
Comment/Recommendation:	
The only manufacturer information on the labeling is the licensed manufacturer, thus the "Manufactured by" was omitted, which is acceptable.	
<i>Recommended labeling practices (U.S. license number for container bearing a partial label)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
U.S. License number 1244 is included.	
<u>Lot number or other lot identification</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	☒ Yes ☐ No ☐ N/A
<u>Expiration date</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<i>Recommended labeling practices references: USP General Chapters <7> Labeling</i> <i>Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<u>Beyond Use Date (Multiple-dose containers)</u>	<u>Acceptable</u>
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A
<u>Product Strength</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
<u>Multiple-dose containers (recommended individual dose)</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55	☐ Yes ☐ No ☒ N/A
<u>Statement: "Rx only"</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	☒ Yes ☐ No

		☐ N/A
Comment/Recommendation: The label is considered a partial label. Thus, the Rx statement is not required. Please note a "partial" label is not required to present all of the information required by regulation due to the size of the label. 21 CFR 610.60 (c) states the information that is required if the label is considered a partial label. The regulation reads "Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."		
<i>Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic</i>		☐ Yes ☐ No ☒ N/A
Comment/Recommendation:		
Medication Guide		Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)		☐ Yes ☐ No ☒ N/A
No Package for container		Acceptable
Regulation: 21 CFR 610.60(b)		☐ Yes ☐ No ☒ N/A
Comment/Recommendation: This product has a container.		
No container label		Acceptable
Regulation: 21 CFR 610.60(d)		☒ Yes ☐ No ☐ N/A
Comment/Recommendation: This container has a label.		
Ferrule and cap overseal (for vials only)		Acceptable
<i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>		☒ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Please confirm there is no text on the ferrule and cap overseal of the vials. October 16, 2019: The applicant confirmed that there is no text on the ferrule or cap overseal and provide a picture with their response.		

(b) (4)	
FDA Response: The applicant's revision is acceptable.	
<u>Visual inspection</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.60(e)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Please confirm that sufficient area of the container remains uncovered for its full length to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located. Please refer to 21 CFR 610.60(e). October 16, 2019: The applicant provided a picture in their response to show the label does the vial and the end user can inspect the contents.	
(b) (4)	
FDA Response: The applicant's revision is acceptable.	
<u>NDC numbers</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: October 16, 2019: The applicant replaced the NDC placeholder with the NDC 0078-0883-61 The NDC is acceptable.	
<u>Route of administration</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	

<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Preparation instructions	Acceptable
Regulation: 21 CFR 201.5(g)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation:	
<i>Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic</i>	☐ Yes ☐ No ☒ N/A
Comment/Recommendation:	
Package type term	Acceptable
<i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Combined DMEPA/OBP comment To Applicant: We recommend revising (b) (4) to read "Single-Dose Vial. Discard Unused Portion." (b) (4) October 16, 2019: The applicant revised the (b) (4) statement to read "Single-Dose Vial. Discard Unused Portion." FDA Response: The applicant's revision is acceptable.	
Misleading statements	Acceptable
Regulation: 21 CFR 201.6	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
To Applicant: Delete the phrase (b) (4) from the side panel. October 16, 2019: The applicant deleted the phrase (b) (4) FDA Response: The applicant's revision is acceptable.	

Prominence of required label statements	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Spanish-language (Drugs)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Bar code label requirements	Acceptable
Regulations: 21 CFR 201.25, 21 CFR 610.67	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<i>Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
Net quantity	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<i>Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99) USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

Statement of Dosage	Acceptable
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: Partial label	
Inactive ingredients	Acceptable
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Partial label	
Storage requirements	Acceptable
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Consider adding storage information to the container label to ensure this important information is accessible to the end user. We recommend stating, "Refrigerate at 2°C to 8°C (36°F to 46°F)". Protect from light. Do not shake or freeze." October 16, 2019: The applicant did not include the storage and handling information as requested. FDA Response: The applicant's revised statement is unacceptable. Therefore, the applicant will be requested to include a "Do not shake" handling condition. To Applicant: Revise your storage and handling statement to read: "Refrigerate at 2°C to 8°C (36°F to 46°F)". Protect from light. Do not shake or freeze." Ensure to include a "Do not shake" handling condition to be consistent with the Prescribing Information. November 1, 2019: The applicant included the handling condition "Do not Shake". FDA Response: The applicant's revision is acceptable.	
Dispensing container	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation:	

Package⁵ Label Evaluation (Carton

(b) (4)

Proper name	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	☒ Yes ☐ No ☐ N/A
Manufacturer name, address, and license number	Acceptable
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: The label includes a manufactured at Novartis Pharma Stein AG statement which is acceptable.	
Lot number or other lot identification	Acceptable
Regulation: 21 CFR 610.61(c)	☒ Yes ☐ No ☐ N/A
Expiration date	Acceptable
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
Beyond Use Date (Multiple-dose containers)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A
Preservative	Acceptable
Regulation: 21 CFR 610.61(e)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Revise the (b) (4) statement to read "No Preservative" per 21 CFR 610.61(e). October 16, 2019: The applicant revised the preservative statement to read "No preservative."	

⁵ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

FDA Response: The applicant's revision is acceptable.	
<u>Number of containers</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.61(f)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<u>Product Strength</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic</i> <i>USP General Chapters: <7> Labeling</i>	☐ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Revise the strength statement to include the total quantity per total volume and the concentration per mL to prevent confusion per USP General Chapters: <7> Labeling. For example: 100 mg/10 mL (10 mg/mL) October 16, 2019: The applicant revised the expression of strength statement as requested. However, the presentation contains extra spaces. FDA Response: The applicant will be requested to delete extra spaces. To Applicant: Please delete extra spacing in the expression of strength to appear as 100 mg/10 mL (10 mg/mL) November 1, 2019: The applicant deleted the extra space in the expression of strength. FDA Response: The applicant's revision is acceptable.	
<u>Storage temperature/requirements</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.61(h)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:	
<i>Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
To Applicant: To highlight important storage information, we recommend revising the storage information to read, "Store and transport vial refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not shake. Do not freeze." October 16, 2019: The applicant did not include the storage and handling information as requested. FDA Response: The applicant's revised statement is unacceptable. Therefore, the applicant will be requested to include a "Do not shake" handling condition. To Applicant: Revise your storage and handling statement to read: "Store and transport vial refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not shake. Do not freeze." Ensure to include a "Do not shake" handling condition to be consistent with the Prescribing Information. November 1, 2019: The applicant included the handling condition "Do not Shake". FDA Response: The applicant's revision is acceptable.	
Handling: "Do Not Shake", "Do not Freeze" or equivalent	Acceptable
Regulation: 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Dr. LemmaDechassa confirmed the drug product needs do not shake, do not freeze and protect from light statements. Refer to the comments under the "Storage temperature/requirements" subsection addressing the handling conditions. November 1, 2019: The applicant included the handling conditions as requested. FDA Response: The applicant's revision is acceptable.	
Multiple dose containers (recommended individual dose)	Acceptable
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation:	

Route of administration	Acceptable
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: <i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Known sensitizing substances	Acceptable
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Dr. LemmaDechassa confirmed that no natural rubber latex or dry natural rubber was used in the manufacture of the product.	
Inactive ingredients	Acceptable
Regulations: 21 CFR 610.61, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Revise the ingredient statement to be consistent with the Prescribing Information. Revise the order of the ingredients and the quantitative information to read: "Each 10 mL vial contains 100 mg crizanlizumab-xxxx, citric acid (5.4 mg), polysorbate 80 (2 mg), sodium citrate (50.5 mg), sucrose (753.3 mg), and water for injection". Please refer to 21 CFR 201.100(b)(5) and USP <1091> Labeling of Inactive Ingredients. October 16, 2019: The applicant revised the ingredient statement as requested. FDA Response: The applicant's revision is acceptable.	
<i>Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Source of the product	Acceptable
Regulation: 21 CFR 610.61(p)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Dr. LemmaDechassa confirmed the source of the product is not a safety issue.	
Minimum potency of product	Acceptable
Regulation: 21 CFR 610.61(r)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	

<u>Rx only</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<u>Divided manufacturing</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation:	
<u>Distributor</u>	<u>Acceptable</u>
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<u>Bar code</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<i>Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
Comment/Recommendation:	
<u>NDC numbers</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<u>Preparation instructions</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.5(g)	☒ Yes

Comment/Recommendation:	☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic</i> <i>USP General Chapters <7> Labeling</i> Comment/Recommendation:	☒ Yes ☐ No ☐ N/A
Package type term <i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> Comment/Recommendation: To Applicant: We recommend revising the statements "(b) (4)" to read "1 Single-Dose Vial. Discard Unused Portion." to serve as the net quantity statement and October 16, 2019: The applicant revised the statements as requested. FDA Response: The applicant's revision is acceptable.	Acceptable ☒ Yes ☐ No ☐ N/A
Misleading statements Regulation: 21 CFR 201.6 Comment/Recommendation: To Applicant: Delete the phrase "(b) (4)" from the principal display panel. October 16, 2019: The applicant deleted the phrase as requested. FDA Response: The applicant's deletion is acceptable.	Acceptable ☒ Yes ☐ No ☐ N/A
Prominence of required label statements Regulation: 21 CFR 201.15 Comment/Recommendation:	Acceptable ☒ Yes ☐ No ☐ N/A
Spanish-language (Drugs) Regulation: 21 CFR 201.16	Acceptable ☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Phenylalanine as a component of aspartame	Acceptable
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A
Sulfitess; required warning statements	Acceptable
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A
Net quantity	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: We recommend revising the statements "(b) (4)" to read "1 Single-Dose Vial. Discard Unused Portion." to serve as the net quantity statement and (b) (4) 	
October 16, 2019: The applicant revised the statements as requested.	
FDA Response: The applicant's revision is acceptable.	
(b) (4)	
<i>Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Statement of Dosage	Acceptable
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A

Dispensing container	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A
Medication Guide	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: This product only has Patient Information.	
Other	Acceptable
	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Consider including the dosage formulation, "injection", directly beneath the proper name on the principal display panel. October 16, 2019: The applicant included the dosage formulation, "injection", directly beneath the proper name on the principal display panel. FDA Response: The applicant's revision is acceptable.	

Prescribing Information and Patient Labeling Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Revised to include the recognized dosage formulation and route of administration per 21 CFR 201.57(a)(2). October 16, 2019: The applicant accepted FDA's proposed Product Title statement. FDA Response: The applicant's revision is acceptable.	
<i>Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: The proposed recommendation uses the preferred format.	
DOSAGE AND ADMINISTRATION	Acceptable
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: No diluents are currently proposed in the Highlights section.	
DOSAGE FORMS AND STRENGTHS	Acceptable
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: OBP Labeling: To Applicant: Revised to provide a concise statement of the dosage formulation and strength per 21 CFR 21.57(a)(8). October 16, 2019: The applicant accepted FDA's proposed Dosage Forms and Strengths statement. FDA Response: The applicant's revision is acceptable.	
<i>Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Proposed revisions address the presentation of the strength. The applicant has applied the term single-dose.	
Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	Acceptable
Regulation: 21 CFR 201.57(c)(3)(iv)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: OBP Labeling: To Applicant: Included a verbatim statement for parenteral drug products per 21 CFR 201.57(c)(3)(iv). The statement reads: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. October 16, 2019: The applicant accepted FDA's insertion of the required statement. FDA Response: The applicant's revision is acceptable.	

Dr. LemmaDechassa confirmed the diluents Sodium Chloride Injection and Dextrose Injection, and the polyvinyl chloride (PVC), polyethylene (PE), and polypropylene (PP) infusion bags are acceptable. Dr. LemmaDechassa also confirmed that no incompatibilities were found with the infusion sets composed of PVC, polyethylene (b) (4)

Dr. LemmaDechassa confirmed the diluted intravenous solution can be mixed gently, but do not shake and the solution is stable for 4.5 hours at room temperature and for 24 hours under refrigeration. Dr. LemmaDechassa confirmed the diluted intravenous solution should be protected from light while stored under refrigeration.

Dr. Reyes Candau-Chacon confirmed the dilution times were acceptable from a microbiology perspective. Also OBP and micro agreed the use of an in-line 0.2 (b) (4) micron filter was acceptable.

To Applicant: Recommend deletion of this messaging, because it can add to confusion as what is considered the "start of preparation" and the total time allowed at RT or under refrigeration until completion of the infusion. The applicant had proposed the wording:

(b) (4)

October 16, 2019: The applicant considered that reflecting the maximum time the vials may be kept at room temperature (prior to piercing) is important to include. The applicant had proposed to clarify the start of preparation to refer to when the vial is first pierced and has included this clarification in Storage Conditions of the Diluted Solution. The applicant has proposed the wording: "Bring vials to room temperature for a maximum of 4 hours prior to the start of preparation (piercing the first vial)." for the Dilution subsection.

FDA Response: Dr. LemmaDechassa confirmed the vial could be allowed to reach room temperature for 4 hours prior to starting the preparation of the diluted solution. The applicant's revisions are acceptable.

To Applicant: Included an additional handling condition for the diluted solution based upon information submitted to the Agency.

The following sentence was recommended for the storage of the diluted solution under refrigeration "Protect the diluted solution from light during storage under refrigeration."

October 16, 2019: The applicant accepted FDA's proposed storage and handling statement to protect the diluted solution from light during storage under refrigeration.

FDA Response: The applicant's revision is acceptable.

To Applicant: Included the reference to positively charged based upon data submitted to the Agency.

The wording for the in-line filter member was revised from (b) (4) to "positively charged polyamide". October 16, 2019: The applicant accepted FDA's insertion of the phrase "positively charged". The applicant also proposed to include "neutral and positively charged" to describe PES filters for completeness. FDA Response: Dr. LemmaDechassa confirmed it is acceptable to include "neutral and positively charged" to describe PES filters. The applicant's revisions are acceptable.	
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products</i> Comment/Recommendation: To Applicant: Revised the names of the diluents to use their official compendial names. October 16, 2019: The applicant accepted FDA's proposal to use the compendial names for the diluents. FDA Response: The applicant's revision is acceptable.	☒ Yes ☐ No ☐ N/A
3 DOSAGE FORMS AND STRENGTHS	
Regulation: 21 CFR 201.57(c)(4) Comment/Recommendation: OBP Labeling: To Applicant: Revised to include the dosage formulation and expressed the strength per the total drug content of the drug product per 21 CFR 21.57(c)(4). October 16, 2019: The applicant accepted FDA's proposed revisions to the Dosage Forms and Strengths statement. FDA Response: The applicant's revision is acceptable.	
<i>Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i> Comment/Recommendation:	☒ Yes ☐ No ☐ N/A
11 DESCRIPTION	
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	
☒ Yes ☐ No ☐ N/A	

Comment/Recommendation:

To Applicant: Revised to include the pharmacologic or therapeutic class per 21 CFR 201.57(c)(12). The first sentence of the Description section was revised to read "Crizanlizumab-tmca is a selectin blocking antibody."

October 16, 2019: The applicant proposed to keep "P" in the description of P-selectin as is consistent with the MOA.

FDA Response: The applicant's revision is acceptable from an OBP perspective. However, additional internal discussions occurred with the OND Division, Clin-Pharm and OBP. The first sentence of the Description section was further revised to read: "Crizanlizumab-tmca is a selectin blocker humanized IgG2 kappa monoclonal antibody that binds to P-selectin."

November 12, 2019: The applicant accepted the proposed revision.

FDA response: The applicant's revision is acceptable.

Dr. LemmaDechassa confirmed the product is sterile, preservative-free, the identifying characteristics and the quantitative and qualitative information.

To Applicant: Revised to include the dosage formulation per 21 CFR 201.57(c)(12) and complete identifying characteristics. Also revised the inactive ingredients to be placed in alphabetical order per USP General Chapters <1091>: Labeling of inactive ingredients in alphabetical order.

October 16, 2019: The applicant accepted FDA's proposed revisions to the second paragraph of the Description section.

FDA Response: The applicant's revision is acceptable.

Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>

☒ Yes
☐ No
☐ N/A

Comment/Recommendation:

OBP Labeling: To Applicant: Revised to include the dosage formulation per 21 CFR 201.57(c)(12) and complete identifying characteristics. Also revised the inactive ingredients to be placed in alphabetical order per USP General Chapters <1091>: Labeling of inactive ingredients in alphabetical order.

October 16, 2019: The applicant accepted FDA's proposed revisions to the second paragraph of the Description section.

FDA Response: The applicant's revision is acceptable.

16 HOW SUPPLIED/ STORAGE AND HANDLING**Acceptable**

Regulation: 21 CFR 201.57(c)(17)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Revised to include a do not shake statement, because the data submitted do not support shaking. Dr. LemmaDechassa confirmed the drug product should be refrigerated, protected from light, do not shake or freeze. October 16, 2019: The applicant indicated that based upon the information previously submitted the "Do Not Shake" is not required within the labeling. FDA Response: FDA disagrees with the applicant's assessment, and the applicant will be requested to include a do not shake statement. To Applicant: The provided data is not adequate to support the removal of the DO NOT SHAKE from the PI. November 1, 2019: The applicant revised the handling conditions to include a "Do not shake" statement. FDA Response: The applicant's revision is acceptable.	
<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Revised to include the dosage formulation per 21 CFR 201.57(c)(17) and delete (b) (4) October 16, 2019: The applicant accepted FDA's proposal to include the dosage formulation and delete (b) (4) from the first paragraph of the How Supplied subsection. FDA Response: The applicant's revisions are acceptable. To Applicant: The drug product is not dispensed for home use and should be under the control of healthcare providers. Thus, this statement appears to be unnecessary. Recommended deletion of the sentence: (b) (4) October 16, 2019: The applicant accepted FDA's deletion of this statement from Section 16. FDA Response: The applicant's revision is acceptable.	

MANUFACTURER INFORMATION		Acceptable
Regulations: 21 CFR 201.100(e), 21 CFR 201.1		☒ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Per 21 CFR 201.1 and 21 CFR 201.100(e), the name and location of business listed here (street address, city, state, and zip code) is required in labeling and should be located after the Patient Counseling Information section, at the end of the PI. If the product has FDA-approved patient labeling that is not a separate document from the PI, the manufacturer information should be located at the end of labeling, after the FDA-approved patient labeling. If the FDA-approved patient labeling is a separate document, or is to be detached and distributed to patients, the manufacturer information should be located both after the Patient Counseling Information section and after the FDA-approved patient labeling. Also refer to 21 CFR 610.61(b). October 16, 2019: The applicant accepted FDA's insertion of the street address "One Health Plaza". FDA Response: The applicant's revision is acceptable.		
<i>Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>		☒ Yes ☐ No ☐ N/A
Comment/Recommendation:		
PATIENT INFORMATION LABELING		
TITLE (NAMES AND DOSAGE FORM)		Acceptable
Regulation for Medication Guide: 21 CFR 208.20(a)(7)		☒ Yes ☐ No ☐ N/A
Comment/Recommendation: <i>21 CFR 208.20(a)(7) The brand and established or proper name of the drug product shall appear immediately below the words "Medication Guide." The established or proper name shall be no less than one-half the height of the brand name.</i>		
<i>Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).</i>		☒ Yes ☐ No ☐ N/A
Comment/Recommendation:		

To Applicant: Revised to include the dosage formulation and route of administration in the title section.

October 16, 2019: The applicant accepted FDA's proposed revisions.

FDA Response: The applicant's revisions are acceptable.

<u>STORAGE AND HANDLING</u>	<u>Acceptable</u>
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Regulation for Medication Guide: 21 CFR 208.20(a)(2)

☐ Yes
☐ No
☒ N/A

Comment/Recommendation:

This product is not provided to the patient for storage or handling.

Recommended labeling practices for Patient Labeling or IFU: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)

☐ Yes
☐ No
☒ N/A

Comment/Recommendation:

<u>INGREDIENTS</u>	<u>Acceptable</u>
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Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)

☒ Yes
☐ No
☐ N/A

Comment/Recommendation:

OBP Labeling: To Applicant: Placed the inactive ingredients in alphabetical order per USP <1091> Labeling of Inactive Ingredients

October 16, 2019: The applicant accepted FDA's proposed revisions.

FDA Response: The applicant's revisions are acceptable.

<u>MANUFACTURER INFORMATION</u>	<u>Acceptable</u>
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21 CFR 201.1, 19 CFR 134.11, 21 CFR 208.20(b)(8)(iii)

☒ Yes
☐ No
☐ N/A

Comment/Recommendation:

OBP Labeling: To Applicant: Per 21 CFR 201.1 and 21 CFR 201.100(e), the name and location of business listed here (street address, city, state, and zip code) is required in labeling and should be located after the Patient Counseling Information section, at the end of the PI. If the product has FDA-approved patient labeling that is not a separate document from the PI, the manufacturer information should be located at the end of labeling, after the FDA-approved patient labeling. If the FDA-approved patient labeling is a separate document, or is to be detached and distributed to patients, the manufacturer information should be located both after the Patient Counseling Information section and after the FDA-approved patient labeling. Also refer to 21 CFR 610.61(b), which references the license number.

October 16, 2019: The applicant accepted FDA's proposed revision.

FDA Response: The applicant's revision is acceptable.

November 1, 2019: The applicant inserted the license number, 1244.

FDA Response: The applicant's revision is acceptable.

*21 CFR 610.61 (add the US license number for consistency with the carton labeling),
21 CFR 610.64 (Name and address of distributor may appear and use a qualifying
phrase for consistency with the carton labeling, when applicable)*

☒ Yes
☐ No
☐ N/A

Comment/Recommendation:

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on November 12, 2019)
<\\cdsesub1\evsprod\bla761128\0048\m1\us\uspi-proposed-clean.docx>
- Patient Information (submitted on November 12, 2019)
<\\cdsesub1\evsprod\bla761128\0048\m1\us\ppi-clean.doc>
- Container Labels (submitted on November 1, 2019)

(b) (4)



Scott
Dallas

Digitally signed by Scott Dallas

Date: 11/12/2019 02:32:56PM

GUID: 508da712000294048aa136a18a6af06a



Mekonnen
Lemma
Dechassa

Digitally signed by Mekonnen Lemma Dechassa

Date: 11/12/2019 03:45:31PM

GUID: 58e50fd5001dab134ff06ffa9107054f

First Approval for Indication/Breakthrough/ Expedited Review: Yes

Recommendation: Approval

BLA STN 761128

Review Number: 1

Review Date: October 24, 2019

Drug Name/Dosage Form	crizanlizumab/injection (ADAKVEO®)
Strength/Potency	100 mg/10 mL in a single-dose vial
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	ADAKVEO® is a P-selectin blocker indicated to prevent and reduce the frequency of vaso-occlusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease
Applicant/Sponsor	Novartis Pharmaceuticals Corporation

Product Overview

Crizanlizumab is a humanized IgG2a/κ monoclonal antibody produced in a Chinese Hamster Ovary (CHO) cell line. Crizanlizumab binds with high affinity to the N-terminal domain of P-selectin on activated platelets or endothelial cells and blocks the interaction of P-selectin with its ligand, P-selectin glycoprotein ligand 1 (PSGL-1). By blocking P-selectin interaction with PSGL-1, crizanlizumab inhibits the interactions between endothelial cells, platelets, sickled red blood cells and leukocytes and prevents vaso-occlusion in patients with sickle cell disease. The potency of crizanlizumab is tested using a cell-based assay that measures the ability of crizanlizumab to block the interaction of PSGL-1 with cells expressing P-selectin on its surface.

Crizanlizumab drug substance is manufactured at Novartis Pharma AG, Basel, Switzerland.

(b) (4)

(b) (4)

Crizanlizumab drug product (DP) is manufactured at Novartis Pharma Stein AG, Stein, Switzerland.

Crizanlizumab DP manufacturing includes

(b) (4)

(b) (4) Data provided in the BLA submission support a DP expiration dating period of 15 months when stored at 2°C to 8°C.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Mekonnen Lemma Dechassa	DBRR III/OBP/OPQ
Drug Product	Mekonnen Lemma Dechassa	DBRR III/OBP/OPQ
Immunogenicity	Joao Pedras-Vasconcelos	DBRR III/OBP/OPQ
Labeling	Scott Dallas	OBP/OPQ
Facility	Zhong Li	DIA/OPF/OPQ
Microbiology (DS)	Maxwell Van Tassell	DMA/OPF/OPQ
Microbiology (DP)	Diane Raccasi	DMA/OPF/OPQ
Business Process Manager	Melinda Bauerlien	RBPMB I/OPRO/OPQ
Team Lead for OBP	Ramesh Potla	DBRR III/OBP/OPQ
Tertiary Reviewer for OBP	Susan Kirshner	DBRR III/OBP/OPQ
Microbiology Team Lead (DS)	Reyes Candau-Chacon	DMA/OPF/OPQ
Microbiology Tertiary Reviewer	Patricia Hughes	DMA/OPF/OPQ
Facilities Team Lead	Peter Qiu	DIA/OPF/OPQ
Application Team Lead	Ramesh Potla	DBRR III/OBP/OPQ

Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
RPM	Michael Gwathmey	DHP/OHOP
Cross-disciplinary Team Lead	Tanya Wroblewski	DHP/OHOP
Medical Officer	Patricia Oneal	DHP/OHOP
Pharm/Tox	Ramadevi Gudi	DHOT/OHOP
Clinical Pharmacology	Xiling Jiang	DCPV/OCF
Statistics	Yaping Wang	DBV/OB

1. Names:

- a. Proprietary Name: Adakveo
- b. Trade Name: Adakveo
- c. Non-Proprietary Name/USAN: crizanlizumab
- d. CAS Name: 1690318-25-2
- e. INN Name: crizanlizumab
- f. OBP systematic name: MAB HUMANIZED (IGG2) ANTIP16109 (LYAM3_HUMAN) [SEG101]
- g. Other names: SelG1, SEG101, NVP-LXI262, (b) (4)

Submissions Reviewed

Submission(s) Reviewed	Document Date
STN 761128/SN0004	05/16/2019
STN 761128/SN0012	07/10/2019
STN 761128/SN0014	07/17/2019
STN 761128/SN0015	07/19/2019
STN 761128/SN0020	08/16/2019
STN 761128/SN0023	08/21/2019
STN 761128/SN0029	09/06/2019
STN 761128/SN0030	09/11/2019
STN 761128/SN0037	09/26/2019
STN 761128/SN0038	10/04/2019
STN 761128/SN0041	10/22/2019
STN 761128/SN0042	10/24/2019

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code ¹	Status ²	Comments
(b) (4)	III	(b) (4)	(b) (4)	3	N/A	Not reviewed. Sufficient information related to compatibility with the product is provided in the BLA.
	III			3	N/A	
	III			3	N/A	
	III			3	N/A	

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows:
2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed).

B. Other documents: None.

3. Consults: None

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Approval.

The Office of Product Quality, CDER, recommends approval of BLA STN 761128 for ADAKVEO[®] (crizanlizumab) manufactured by Novartis Pharmaceuticals Corporation. The data submitted in this application are adequate to support the conclusion that the manufacture of ADAKVEO[®] is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

Manufacturing location:

- Drug Substance: Novartis Pharma AG, Basel, Switzerland.
 - Drug Product: Novartis Pharma Stein AG, Stein, Switzerland.
- Fill size and dosage form – 100 mg/10 mL (10 mg/mL) solution in a single-dose vial
- Dating period:
 - Drug Product: 15 months; at 2-8 °C
 - Drug Substance: (b) (4) months; at (b) (4) °C
 - Stability Option:
 - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release
 - Yes, ADAKVEO[®] is exempted from lot release per FR Doc. 95–29960. Well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products are exempted from 21 CFR 601.2a lot release requirements.
 - Novartis Pharmaceutical Corporation requested a categorical exclusion from the requirements of an environmental assessment under 21 CFR 25.31(c). The claim of a categorical exclusion is accepted.

C. Benefit/Risk Considerations:

ADAKVEO® (crizanlizumab) is indicated to prevent and reduce the frequency of vaso-occlusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease.

The data submitted in this application support the conclusion that the manufacture of crizanlizumab is well controlled and yields a consistently high-quality product. Results show conditions used in manufacturing were sufficiently validated, and a consistent product was prepared from the multiple production runs presented. From a product quality perspective, this product is approvable for human use. Review of manufacturing has identified that the methodologies used for drug substance and drug product manufacturing, release, and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The drug substance manufacturing process is robust (b) (4)

The binding affinity assay by SPR provided in BLA show that crizanlizumab binds to FcγRIIa^{HR} and FcγRIIa^{LR} with micromolar affinity, which is sufficient to drive effector functions. Crizanlizumab can bind endothelial cells and activated platelets and FcγRIIa expressed on myeloid cells (monocytes/neutrophils) simultaneously and can trigger phagocytosis and cytotoxicity, which can result in endothelium damage and platelets depletion. The antibody-dependent cellular cytotoxicity (ADCC) activity data provided in the BLA addresses natural killer (NK) cell-mediated ADCC and did not address the myeloid cell-dependent ADCC and antibody-dependent cellular phagocytosis (ADCP) effector activities that can be induced by crizanlizumab Fc. The contribution of this myeloid cell-dependent effector mechanism should be investigated because FcγRIIa is the most widely expressed FcγR on myeloid cells and therefore, may reflect an additional mechanism of action or toxicity for crizanlizumab. The purpose of Post-Marketing Requirement (PMR) 1, as described in Section B below, is to demonstrate whether crizanlizumab induces myeloid cell-dependent effector functions using (b) (4) and as appropriate, establish a control strategy to monitor ADCC or ADCP.

The drug product specifications currently include testing for endotoxins per USP <85>. The USP <85> Bacterial Endotoxin Test (BET) is not capable of detecting endotoxin in drug product at release. Endotoxin spiking studies with drug product indicate that the USP <85> BET detects less than 50% of the nominal amount of spiked endotoxin. However, this is not an approvability issue because the applicant has agreed, as *an interim* measure, to test endotoxin in drug product using a USP Pyrogen Test <151>. The USP Pyrogen Test is appropriate as *an interim* measure because studies in rabbits indicate that drug product samples spiked with endotoxin are pyrogenic (cause fevers) in rabbits. The Sponsor agreed to Post-Marketing Commitment (PMC) 1, described in Section B below, to develop and implement a more reliable *in vitro* drug product endotoxin release test method to detect endotoxins in drug product. (b) (4)

The current drug substance (DS) and drug product (DP) release and stability specifications are based on limited clinical and manufacturing experience, i.e., phase 1 and phase 2 studies. The Sponsor is currently conducting a phase 3 clinical study CSEG101 A2301 to further evaluate the safety and efficacy of crizanlizumab. The goal of PMC 2, as described in Section B below, is to make appropriate revisions to the DS and DP specifications to incorporate the experience gained from the phase 3 study.

The Applicant provided a shipping validation protocol (b) (4) in the BLA, but did not describe when the studies will be conducted and whether the validation results will be provided to the Agency. The goal of PMC 3, as described in Section B below, is to perform real time shipping validation studies to evaluate the impact of shipment on the product quality of crizanlizumab drug product.

The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective. We also recommend approval of the commercial manufacture of crizanlizumab drug substance at Novartis Pharma AG, Basel, Switzerland, and commercial manufacture of crizanlizumab drug product at Novartis Pharma Stein AG, Stein, Switzerland. The OBP product quality and immunogenicity, DMA microbiological drug substance and drug product, DIA facility, and OBP labeling technical assessments are located as separate documents in Panorama.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

PMR 1: Demonstrate whether crizanlizumab induces myeloid cell-dependent effector functions using (b) (4). If cell-dependent effector functions are identified as confirmed or potential activities for crizanlizumab, develop and implement an appropriate control strategy, that monitors antibody-dependent cellular cytotoxicity or antibody-dependent cellular phagocytosis.

PMC 1: Develop an endotoxin detection method capable of detecting endotoxin from the DP release samples.

PMC 2: Revise the release and stability specifications for crizanlizumab drug substance (DS) and drug product (DP) based on the product quality attribute test results of clinical batches used in phase 3 clinical study CSEG101 A2301. Provide the revised specifications in the efficacy sBLA submission for clinical study CSEG101 A2301.

PMC 3: Perform real time shipping validation studies, per (b) (4) to support the stability of crizanlizumab drug product vials from the drug product manufacturing facility in Switzerland to the US..

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to both drug substance and drug product.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
Identity (identity)	Process, DS and DP failures	Intrinsic to the molecule	(b) (4)	N/A
Potency (potency)	Process, DS and DP failure	Intrinsic to the molecule, (b) (4)		Data from characterization studies show that crizanlizumab binds to FCγRIIa receptor with a micromolar affinity, which is sufficient to drive effector functions. FCγRIIa receptor is predominantly expressed on cells of myeloid origin. The Sponsor did not evaluate whether crizanlizumab induces myeloid cell-dependent effector functions, which can result in endothelium damage and platelets depletion. A post-marketing requirement will be communicated to the Sponsor to evaluate whether crizanlizumab induces myeloid cell-dependent antibody-dependent cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP).
pH	Safety and efficacy	General CQA		N/A
Aggregates (product-related impurity)	Immunogenicity	(b) (4) on stability		The current DS and DP control strategy is based on limited clinical and manufacturing experience, i.e., phase 1 and phase 2 studies. The Sponsor is currently conducting a phase 3 clinical study CSEG101 A2301 to further evaluate the safety and efficacy of crizanlizumab in sickle cell patients. A post-marketing commitment will be communicated to the Sponsor to make appropriate revisions to the DS and DP specifications to incorporate the experience gained from the phase 3 study.
Fragments (product-related impurity)	Safety and efficacy	Degradation on stability		
(b) (4) (product-related impurity)	Safety (potential risk for immunogenicity) No impact of (b) (4) on potency	(b) (4)		
(b) (4) (product-related impurity)	(b) (4)	(b) (4)		

B. Drug Substance [crizanlizumab] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA	Type Source/Introduction	Risk	Control Strategy	Other
Binding of crizanlizumab to P-selectin	Intrinsic to the molecule	Directly linked to efficacy	(b) (4)	The proposed control strategy provides an acceptable assurance of efficacy (potency)
Higher order structure	Intrinsic to the molecule	Could influence potency, PK / PD, immunogenicity		The proposed control strategy provides an acceptable assurance of efficacy (potency) and safety
Affinity / binding to Fc receptors	Intrinsic to the molecule	Potency and safety		(b) (4) [Redacted] [Redacted] [Redacted] [Redacted] [Redacted] [Redacted] [Redacted] [Redacted] As described in Table I

				(b) (4) above, a PMR will be communicated to the Sponsor to further characterize whether crizanlizumab drives myeloid cell-dependent effector functions in an appropriate cell-based assay.
(b) (4)	(b) (4)	(b) (4)		(b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) the Sponsor will be asked to provide a PMC to revise the DS and DP specifications to reflect the experience gained from the ongoing phase 3 study, in order to ensure that the new specifications are appropriately aligned with both manufacturing and pivotal Phase 3 clinical experience.
		(b) (4)		Review of product quality data from all (b) (4)
		Safety- effector function and immunogenicity		
Host Cell Proteins (HCP)	(b) (4)	Safety		The proposed control strategy provides an acceptable assurance of safety.

Residual DNA	(b) (4)	Safety	(b) (4)	N/A
(b) (4)	(b) (4)	Safety	(b) (4)	N/A

			(b) (4)	
Bioburden	Contamination Bioburden can be introduced throughout the manufacturing process (raw materials and environment).	Safety		<i>The proposed control strategy provides an acceptable assurance of safety.</i>
Endotoxin	Contamination Endotoxin can be introduced throughout the manufacturing process (raw materials and environment).	Safety		<i>The proposed control strategy provides an acceptable assurance of safety.</i>
Mycoplasma	Contamination Mycoplasma can be introduced during (b) (4)	Safety		<i>The proposed control strategy provides an acceptable assurance of safety.</i>
Adventitious Virus	Contamination Adventitious virus can be introduced (b) (4)	Safety		<i>The proposed control strategy provides an acceptable assurance of safety.</i>
(b) (4)	Process-related impurities (b) (4)	Safety		<i>The proposed control strategy provides an acceptable assurance of safety.</i>

- Description:
ADAKVEO® (crizanlizumab) is a humanized IgG2a/κ monoclonal antibody produced in a Chinese Hamster Ovary cell line (CHO-(b) (4)). Crizanlizumab binds to the N-terminal (lectin) domain of P-selectin and prevent interaction to its receptors. Crizanlizumab consists of two heavy chains (HC) and two light chains (LC). It was generated by (b) (4)

- Mechanism of Action (MoA):**
Crizanlizumab binds to the N-terminal domain of P-selectin on activated platelets or endothelial cells expressing P-selectin with a nanomolar affinity and blocks the interaction of P-selectin with its ligand, P-selectin glycoprotein ligand 1 (PSGL-1). PSGL-1 is a receptor for P-selectin and is expressed on myeloid cells (red blood cells, platelets, granulocytes, monocytes) and stimulated T lymphocytes. By blocking P-selectin interaction with PSGL-1, crizanlizumab inhibits the interactions between endothelial cells, platelets, sickled red blood cells and leukocytes and prevents vaso-occlusion in patients with sickle cell disease.
- Potency Assay:**
The potency testing of crizanlizumab involves a cell-based assay that measures the ability of crizanlizumab to block the interaction PSGL-1 with cells expressing P-selectin on its surface. The assay is performed by coating V-shaped microtiter plate with recombinant human PSGL-1, blocking non-specific surface interaction and adding increasing concentrations of crizanlizumab. Raji cells expressing human P-selectin are fluorescently labelled (by calcein dye) and added to the PSGL-1 coated plate and incubated to allow the binding of the cells to PSGL-1. The plate is centrifuged, and unattached cells (to the coated PSGL-1) accumulate in the bottom of the V-shaped wells where they are detected using a fluorescence reader. The inhibition of the interaction of the cells to coated PSGL-1 increases the number of cells (fluorescent signal) at the bottom of the well in a crizanlizumab concentration dependent reaction. The relative potency of the test sample is determined by comparing with the reference standard after the signal is normalized for protein content. The relative potency is calculated using a parallel line assay according to USP <1034> and Ph.Eur.5.3. The assay is proposed for evaluating potency and identity testing of crizanlizumab DS and DP at release and on stability at Novartis Basel site.

- Reference Materials:**

(b) (4)

- Critical starting materials or intermediates:**

(b) (4)

- Manufacturing process summary:

(b) (4)

- Container closure:

(b) (4)

- Dating period and storage conditions:

(b) (4)

C. Drug Product [crizanlizumab] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk and Lifecycle Knowledge Management

CQA	Type Source/Introduction	Risk	Control Strategy	Other
Protein content	General CQA Protein concentration is influenced by DP (b) (4)	Safety and Efficacy	(b) (4)	N/A
Sterility and container closure integrity	Sterility could be compromised by contaminants introduced throughout drug product manufacturing or through a container closure integrity failure.	Safety		<i>The proposed control strategy provides an acceptable assurance of safety.</i>
Endotoxin	Contaminant that could be introduced throughout drug product manufacturing or due to a container closure integrity failure.	Safety		<i>The USP <85> Bacterial Endotoxin Test (BET) is not capable of detecting endotoxin in drug product at release. However, this is</i>

				not an approvability issue because the applicant has agreed, as an interim measure, to test endotoxin in drug product using a USP Pyrogen Test <151>. The USP Pyrogen Test is appropriate as an interim measure because studies in rabbits indicate that drug product samples spiked with endotoxin are pyrogenic (cause fevers) in rabbits. The Sponsor has agreed to a post-Marketing Commitment to develop and implement a more reliable in vitro drug product endotoxin release test method capable of detecting endotoxins in drug product.
Particulate matter and subvisible particles	Particulate matter could form throughout manufacturing and during DP storage	Safety	(b) (4)	The proposed control strategy provides an acceptable assurance of safety.
Appearance	General CQA Appearance could be impacted by formulation or indicate changes in product such as degradation	Safety and efficacy		The proposed control strategy is acceptable.
Extractable Volume	General CQA most likely impacted by the (b) (4)	Safety and efficacy		The proposed control strategy is acceptable.
Osmolarity	General COA influenced by (b) (4) No change is expected on stability.	Safety	(b) (4)	N/A
(b) (4)				The proposed control strategy is acceptable.

	(b) (4)		(b) (4)
Leachables	Leachables could potentially be introduced by any product contact equipment, container closure and consumables	Safety	<i>The proposed control strategy provides an acceptable assurance of safety.</i>

- Potency and Strength:**
 Crizanlizumab is supplied at 100 mg/10 mL in a single-dose vial. Potency is defined as the percent activity relative to the current crizanlizumab reference standard. The potency assay is the same as described in the DS section of this review memo.
- Summary of Product Design:**
 Crizanlizumab is supplied as a sterile, preservative-free solution in a single-dose vial for intravenous infusion. Crizanlizumab DP is formulated at 100 mg/10 mL in (b) (4) sucrose (753.3 g), (b) (4) sodium citrate (50.53 g), (b) (4) polysorbate 80 (2.0 g), pH 6.0.
- List of Excipients:**
 Excipients include (b) (4) sucrose, (b) (4) sodium citrate, and (b) (4) polysorbate 80.
- Reference Materials:**
 (b) (4)
- Manufacturing process summary:**
 (b) (4)
- Container closure:**

The primary container closure system for crizanlizumab DP consists of a 10 mL Type I clear glass vial (b) (4)

(b) (4) rubber stopper (b) (4) and aluminum flip-off cap with a yellow plastic flip-off disk.

- Dating period and storage conditions:
The dating period for crizanlizumab DP is 15 months when stored at 2°C to 8°C, protected from light.

D. Novel Approaches/Precedents: None.

E. Any Special Product Quality Labeling Recommendations:

- Store in a refrigerator at 2°C to 8°C (36°F to 46°F).
- Protect from light until use.
- Do not freeze. Do not shake.

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Crizanlizumab DS - Manufacturing, IPC, Quality control, Stability. Preparation and storage sites for WCB and MCB. Crizanlizumab DP - QC, Stability testing	Novartis Pharma AG Lichtstrasse 35, Basel, Switzerland, 4056	3002807772	Pre-license inspection requested	VAI	Approve
Crizanlizumab DS (b) (4)	(b) (4)	(b) (4)	Approve - Based on Previous History	N/A	Approve
Crizanlizumab DS (b) (4)	(b) (4)	(b) (4)	Approve - Based on Previous History	N/A	Approve
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Crizanlizumab DP - Manufacturing, IPC testing and primary packaging, QC, Stability testing, secondary packaging and storage. Crizanlizumab DS - Storage	Novartis Pharma Stein AG Schaffhauserstrasse, Stein, Switzerland, 4332	3002653483	Approve - Based on Previous History	PLI Waived	Approve
(b) (4)	(b) (4)	(b) (4)	Approve - Based on	N/A	Approve

(b) (4)	Previous History		
	Approve - Based on Previous History	N/A	Approve
	No Evaluation Necessary	N/A	N/A

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Novartis Pharma AG (FEI 3002807772) and Novartis Pharma Stein AG (FEI 3002653483), proposed for crizanlizumab DS and DP manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facility standpoint.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols:

1. Validation of (b) (4) at Commercial Scale
2. Qualification and Requalification of Reference Materials
3. Qualification and Requalification of Working Cell Banks
4. Annual Stability Protocol

ii. Outstanding review issues/residual risk:

See outstanding review issues summarized in Drug Product section below.

iii. Future inspection points to consider:

1. Adequacy of method verification for compendial methods used for DS lot release and stability testing.
2. Performance of DS release and stability tests should be evaluated. The system suitability test (SST) requirements (b) (4)

(b) (4) are appropriately investigated and managed by the firm.

b. Drug Product

i. Protocols:

1. Annual Stability Protocol
2. Qualification and Requalification of Reference Material (same as DS)

ii. Outstanding review issues/residual risk:

Post-marketing requirement to characterize the myeloid cell-dependent effector functions by crizanlizumab; post-marketing commitments to revise the DS and DP release and stability specifications based on experience gained from ongoing phase 3 clinical study; perform real-time shipping validation studies to evaluate the impact of shipment on crizanlizumab drug product, develop a suitable endotoxin method for the release testing of crizanlizumab DP.

iii. Future inspection points to consider:

1. Adequacy of method verification for compendial methods used for DP lot release and stability testing.
2. Performance of DP release and stability tests should be evaluated. The system suitability test (SST) requirements for (b) (4) are appropriately investigated and managed by the firm.



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BLA: STN 761128

Crizanlizumab

Novartis Pharmaceuticals Corporation

Mekonnen Lemma Dechassa, Ph.D., Biologist
Ramesh Potla, Ph.D., Team Lead

Division of Biotechnology Research and Review III

OBP CMC Review Data Sheet

1. **BLA#** STN 761128

2. **REVIEW DATE:** 10/23/2019

3. **PRIMARY REVIEW TEAM:**

a. Medical Officer/ Clinical Reviewer:	Tanya Wroblewski, Patricia Oneal, Rosanna Setse
b. Pharm/Tox:	Rama Gudi, Christopher Sheth
c. Product Quality:	Mekonnen Lemma Dechassa, Joao Pedras-Vasconcelos, Ramesh Potla, Susan Kirshner
d. Product Quality Microbiology:	Maxwell Van Tassell, Diane Raccasi, Maria Candauchacon
e. Facilities:	Zhong Li, Peter Qiu
f. Clinical Pharmacology:	Olanrewaju Okusanya, Xiling Jiang
h. Statistics:	Yaping Wang, Yeh-Fong Chen
i. OBP Labeling:	Scott Dallas
j. OND RPM:	Michael Gwathmey
k. OPQ RBPM:	Melinda Bauerlien

4. **MAJOR GRMP DEADLINES:**

a. Filing Meeting:	July 14, 2019
b. Mid-cycle meeting:	August 16, 2019
c. Wrap-up meeting:	October 15, 2019
d. Primary review due:	October 23, 2019
e. Secondary review due:	October 28, 2019
f. PDUFA action date:	November 16, 2019

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document:	Date:
Filing Letter	July 15, 2019
Post mid-cycle communication	September 10, 2019
Sponsor Teleconference	October 16, 2019
Information Request 1	June 21, 2019
Information Request 2	July 12, 2019
Information Request 3	August 2, 2019
Information Request 4	August 20, 2019

Information Request 5	September 16, 2019
Information Request 6	October 8, 2019

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
Module 3 Rolling Submission Original BLA	May 16, 2019	Yes
CMC amendment	September 11, 2019	Yes
Response to IR 1	July 10, 2019 July 17, 2019	Yes
Response to IR 2	July 19, 2019 August 16, 2019	Yes
Response to IR 3	August 21, 2019	Yes
Response to IR 4	September 06, 2019	Yes
Response to IR 5	October 4, 2019	Yes
Response to IR 6	October 22, 2019	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

a. Proprietary Name:	Adakveo
b. Trade Name:	Adakveo
c. Non-Proprietary Name/USAN:	crizanlizumab
d. CAS Name:	1690318-25-2
e. Common Name:	crizanlizumab
f. INN Name:	crizanlizumab
g. Compendial Name:	N/A
h. OBP systematic name:	MAB HUMANIZED (IGG2) ANTIP16109 (LYAM3_HUMAN) [SEG101]
i. Other names:	SelG1, SEG101, NVP-LXI262, (b) (4)

8. PHARMACOLOGICAL CATEGORY: Therapeutic recombinant humanized anti-P-selectin monoclonal antibody

9. DOSAGE FORM: Injection

10. STRENGTH/POTENCY:

- (i): The concentration/strength of the Drug Product: 100 mg/10 mL in a single-use vial.
- (ii): Type of potency assay(s): Potency is defined as the percent activity relative to the reference material using an assay for inhibition of adhesion of P-selectin expressing cells to P-selectin ligand (PSGL-1).

11. ROUTE OF ADMINISTRATION: Intravenous infusion

12. REFERENCED DRUG MASTER FILES (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
		(b) (4)	Yes	Information in the BLA was adequate; no separate review was required.
			Yes	Information in the BLA was adequate; no separate review was required
			Yes	Information in the BLA was adequate; no separate review was required
			Yes	Information in the BLA was adequate; no separate review was required

13. INSPECTIONAL ACTIVITIES:

A pre-license inspection (PLI) was conducted between August 21, 2019 and August 29, 2019 of Novartis Pharma (Basel, Switzerland), the drug substance manufacturing facility for crizanlizumab. The inspection was conducted by (b) (4) and covered the manufacturing operations and testing of crizanlizumab including the following five quality systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls.

A 4-item FDA-483 was issued. See Appendix 1 for a copy of FDA-483. Both the initial and final classification of the inspection is “Approval”. The Agency waived the PLI of Novartis Pharma (Stein, Switzerland), the DP manufacturing facility for crizanlizumab based on the facility’s compliance history, current acceptable GMP status (b) (4) (see Appendix 2 for a waiver memo by Zhong Li, OPQ/DIA).

14. CONSULTS REQUESTED BY OBP: None

15. QUALITY BY DESIGN ELEMENTS:

The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
x	Design of Experiments
x	Formal Risk Assessment/Risk Management
x	Multivariate Statistical Process Control
	Process Analytical Technology

Expanded Change Protocol

DOE, univariate studies and multivariate statistical analysis were submitted in support of process development and assessment of control strategies for DS and DP manufacturing. Sponsor conducted risk assessments for the DS and DP manufacturing processes using FMEA. Process parameters (PP) were classified as critical process parameter (CPP), key process parameter (KPP) or non-key process parameter (NKPP) based on their impact on critical quality attribute (CQA) and process performance. CPP is a PP that impact the CQA of the product and should be monitored or controlled to ensure product quality. KPP impacts process performance (process indicator-PI) and should monitored or controlled to maintain consistency of process performance, and NKPP is a PP that is considered has no impact on a CQA or PI. The PP identified were evaluated by process characterization studies and proven acceptance ranges (PAR) were established to support the overall control strategies for crizanlizumab.

16. PRECEDENTS: None

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The data submitted in this Biologics License Application support the conclusion that the manufacture of Adakveo® (crizanlizumab-tmca) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. It is recommended that Adakveo® (crizanlizumab-tmca) be approved for human use (under conditions specified in the package insert).

II. List of Deficiencies to be Communicated

N/A

III. List of Post-Marketing Commitments/Requirements

1. Rationale: The binding affinity assay by SPR provided in BLA shows that crizanlizumab binds to FcγRIIa^{HR} and FcγRIIa^{LR} with micromolar affinity, which is sufficient to drive effector functions. Crizanlizumab can bind endothelial cells and activated platelets and FcγRIIa expressed on myeloid cells (monocytes/neutrophils) simultaneously and can trigger phagocytosis and cytotoxicity, which can result in endothelium damage and platelets depletion. The antibody-dependent cellular cytotoxicity (ADCC) activity data provided in the BLA addresses natural killer (NK) cell-mediated ADCC and did not address the myeloid cell-dependent ADCC and antibody dependent cellular phagocytosis effector activities that can be induced by crizanlizumab Fc. The contribution of this myeloid cell-dependent effector mechanism should be investigated because FcγRIIa is the most widely expressed FcγRIIa on myeloid cells and therefore, may reflect an additional mechanism of action or toxicity for crizanlizumab. To address this concern, the Agency proposes the following:

Draft PMR: Demonstrate whether crizanlizumab induces myeloid cell-dependent effector functions using (b) (4). If cell-dependent effector functions are identified as confirmed or potential activities for crizanlizumab, develop and implement an appropriate control strategy, that monitors antibody-dependent cellular cytotoxicity or antibody-dependent cellular phagocytosis. The final study report will be submitted in accordance with 21 CFR 601.12.

2. Rationale: The Applicant provided a shipping validation protocol in the BLA but did not describe when the studies will be conducted and whether the validation results will be provided to the Agency. The goal of the study will be to evaluate the impact of shipment on the product quality of crizanlizumab drug product.

Draft PMC: To perform real time shipping validation studies, per (b) (4) to support the stability of crizanlizumab drug product vials from the drug product manufacturing facility in Switzerland to the US. Final study report submission: {Month} {Date}, 2020.

3. Rationale: The current DS and DP release and stability specifications are based on limited clinical and manufacturing experience, i.e., phase 1 and phase 2 studies. The Sponsor is currently conducting a phase 3 clinical study to further evaluate the safety and efficacy of crizanlizumab. The goal of this PMC is to make appropriate revisions to the DS and DP specifications to reflect the experience gained from the pertinent phase 3 study. The following PMC is proposed to address this concern:

Draft PMC: Revise the release and stability specifications for crizanlizumab drug substance (DS) and drug product (DP) based on the product quality attribute test results of clinical batches used in phase 3 clinical study CSEG101 A2301. Provide the revised specifications in the efficacy sBLA submission for clinical study CSEG101 A2301.

IV. Review of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion

A claim for a categorical exclusion is being made under 21 CFR 25.31 (c) for substances that occur naturally in the environment. Crizanlizumab drug product contains excipients which are naturally occurring or nonhazardous. The active pharmaceutical ingredient (monoclonal antibody) contains only naturally occurring amino acids that is catabolized and absorbed into the body and is not expected to result in any significant risk to the environment. The claim of categorical exemption is accepted.

V. Primary Container Labeling Review

The Primary and secondary container labeling review was performed by CAPT Scott Dallas, OBP.

VI. Review of Common Technical Document- Quality Module 3.2

This document contains the review of information provided on crizanlizumab drug substance (section 3.2.S), drug product (section 3.2.P), adventitious agents safety evaluation (section 3.2.A), and the method validation package and batch records (section 3.2.R). Crizanlizumab drug substance is Manufactured at Novartis Pharma (Basel, Switzerland) and drug product is manufactured at Novartis Pharma (Stein, Switzerland).

Crizanlizumab is expressed in Chinese Hamster Ovary (CHO) cell line. (b) (4)

(b) (4)

(b) (4) The container closure is a single-use 10 mL type I glass vial with a (b) (4) rubber stopper (b) (4) and sealed aluminum cap.

VII. Review of Immunogenicity Assays- Module 5.3.1.4

The immunogenicity assays in section 5.3.1.4 are reviewed by Dr. Joao Pedras-Vasconcelos and are described in a separate review memo.

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351(a) BLA IMMUNOGENICITY ASSESSMENT

Application Type	BLA
Application Number	761128
Submit Date	May 16, 2019
Received Date	May 16, 2016
PDUFA Goal Date	November 16, 2019
Division/Office	DHP
Review Completion Date	September 24, 2019
Product Code Name	SEG101/SelG1
Proposed Proper Name¹	Crizanlizumab-tmca
Proposed Proprietary Name¹	ADKAVEO
Pharmacologic Class	P-Selectin antagonist
Applicant	Novartis Pharmaceuticals, Corp.
Applicant Proposed Indication(s)	Prevention of vaso-occlusive events resulting from Sickle Cell Disease (SCD)
Recommended Regulatory Action	Approval

Immunogenicity Assessors

Primary Reviewer(s)	Joao Pedras-Vasconcelos, Ph.D
Secondary Reviewer(s)	Susan Kirshner, Ph.D, Review Chief
Tertiary Reviewer(s)	NA

¹ The proposed proper and proprietary names are conditionally accepted until such time that the application is approved.

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1. Summary Basis of Recommendation/Executive Summary

1.1 Immunogenicity Executive Summary and Recommendation

Crizanlizumab is a humanized IgG2 kappa monoclonal antibody (mAb) that binds to P-selectin with high affinity and blocks cognate interactions with its ligands CD162/PSGL-1 and sialylated Lewis-X oligosaccharide. Crizanlizumab is proposed for the treatment of sickle cell disease (SCD) to reduce occurrence of vascular-occlusive events (VOC) by inhibiting the P-selectin mediated cellular adhesive interactions that are a key factor in the pathogenesis of VOC. Crizanlizumab was originally developed by Reprixys Pharmaceuticals which termed the product SelG1. Following the acquisition of Reprixys by the applicant Novartis Pharmaceutical Corp, the product was termed SEG101. Crizanlizumab has breakthrough designation and an accelerated development pathway. Therefore, phase 3 studies have not yet been completed, and limited immunogenicity data derived from two phase 1 PK/PD studies

(CSEG101 A2101 and A2102) in healthy volunteers and two phase 2 clinical studies in patients with SCD (CSEG101 A2201 and A2202) are available. A Phase 3 efficacy study, CSEG101 A2301, is currently ongoing and will provide additional efficacy, safety and immunogenicity data. Novartis will use the recommended tiered approach of screening, confirmatory, titering and neutralizing antibody assays to analyze resulting immunogenicity data which will be submitted post-approval.

Reprixys Pharmaceuticals, the original developer of crizanlizumab, used a single tiered qualitative Amplified luminescent proximity homogeneous assay (AlphaLISA) developed by (b) (4) to detect the anti-SELG1 in the serum samples from clinical studies A2101(PK/PD in healthy volunteers) and A2201 (efficacy/safety in patients with SCD). The anti-drug antibody (ADA) assay was a fit-for-purpose assay for testing phase 1 and 2 study samples and was never completely validated. This assay was discontinued and although Novartis owns the immunogenicity data obtained using this assay, they do not have access to the assay itself, and no further experimental validation is possible at this time without performing a new validation exercise. Novartis reevaluated data mathematically based on predose sample signal to negative control ratios from individual study samples and determined that (b) (4) 10/137 (7.0%) patients in study A2201 were anti-drug antibody (ADA) positive. (b) (4)

(b) (4)

(b) (4)

(b) (4)

Novartis, the applicant, used a tiered approach for ADA testing including screening, confirmatory, and titering assays to detect anti-SEG1 antibodies in the serum samples from clinical studies CSEG101A2102 (PK/PD in Healthy volunteers) or CSEG101A2202 (SCD). Novartis contracted the development of a MesoScale Discovery (MSD) platform electrochemiluminescence (ECL) bridging ELISA to (b) (4). The assay was validated for use with healthy volunteer sera and SCD sera and is suitable for its intended purpose. Using this assay, 2/67 (2.99%) healthy volunteer sera tested positive for ADA after treatment in study A2102, while no sera from patient with SCD tested positive for in study A2202. A neutralizing antibody (NAb) assay is currently under development and will be used to test confirmed ADA+ samples in their phase 1 and 2

(b) (4)

Novartis' initial immunogenicity label in section 6.2 Immunogenicity (b) (4) Following an information request to limit ADA data in section 6.2 to ADA data derived from validated MSD bridging ELISA. The current proposed label section 6.2 includes ADA rates from studies A2102 (1/61=1.6%) and A2202 (0/45) in separate paragraphs and used the validated MSD ELISA data.

There are no approvability issues arising from our immunogenicity assessment. We recommend four post-marketing commitments related to immunogenicity:

- 1) The applicant should develop and validate a neutralizing anti-drug antibody assay (NADA) to test confirmed anti-drug antibody (ADA) positive samples from studies CSEG101 A2102, A2202 and A2301.

- 2) The applicant should assess NADA responses in all confirmed ADA positive samples from studies CSEG101 A2102, A2202 and A2301 using the validated NADA assay from PMC 1.
- 3) The applicant should assess the immunogenicity of crizanlizumab, including ADA and NADA in all subjects in Study CSEG101 A2301 using validated assays.
- 4) The applicant should submit an Integrated Summary of Immunogenicity that describes the totality of their immunogenicity program, including results for phase III clinical study CSEG101 A2301.

1.2 Deficiencies and Other Recommended Comments to Applicant

No deficiencies. There will be four immunogenicity related PMCs

- 1) Develop and validate a neutralizing antibody assay (NADA) to test confirmed anti-drug antibody positive samples from studies CSEG101 A2102, A2202 and A2301. The assay should be capable of detecting NADA responses in the presence of crizanlizumab levels that are expected to be present in the serum at time of subject sampling.
- 2) Assess Neutralizing anti-drug antibody (NADA) responses with a validated NADA assay (requested in PMC X). NADA response will be evaluated in all confirmed ADA positive samples from studies CSEG101 A2102, A2202 and A2301. Include information on the level of crizanlizumab in each sample at each sampling point.
- 3) Assess immunogenicity of crizanlizumab, including anti-drug antibodies (ADA) and neutralizing anti-drug antibodies (NADA) in all crizanlizumab-treated subjects in Study A2301. In the final study report include: the complete immunogenicity data set, information on the drug product lots administered to each patient, the ADA status and titers, the NADA status and the level of drug in each patient's test sample at the specific sampling point.
- 4) Submit an Integrated Summary of Immunogenicity that describes the totality of the immunogenicity program, as recommended in Section VIII Documentation of the 2019 FDA Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection. Submit the ISI report to eCTD Section 5.3.5.3 Reports of Analysis of Data from More than One Study. Update ADAKVEO label with the updated immunogenicity information

Assessor comment:

Final wording for proposed PMCs was not finalized at time the current immunogenicity memo was completed, as it involves input from both OBP and OCP.

2. Assessment

Document Reviewed	Submission Date	Assessment Completed
BLA 761128 SN 04	May 16, 2019	yes
BLA 761128 SN 10	July 10, 2019	yes
BLA 761128 SN 27	Aug 30, 2019	yes

BLA 761128 SN 35	Sept 16, 2019	yes
BLA 761128 SN 40	October 17, 2019	yes

2.1 Immunogenicity Risk Assessment

Crizanlizumab (SelG1/SEG101) is a humanized IgG2 kappa monoclonal antibody (mAb) that binds to P-selectin with high affinity and blocks interactions with its ligands (PSGL-1/CD162, sialylated Lewis-X oligosaccharide). Crizanlizumab is proposed for the treatment of sickle cell disease (SCD) patients to reduce occurrence of vascular-occlusive events (VOC) by inhibiting the P-selectin mediated cellular adhesive interactions that are a key factor in the pathogenesis of VOC. The environment in SCD is characterized by high levels of innate inflammatory cytokines such as IL-6, IL-8, TNF, and IL-1, and increased complement activation, especially during VOC. Patients with SCD also have reported high rates of auto-antibodies, including anti-heme, anti-nuclear, anti-cardiolipin antibodies and rheumatoid factor. Although the product itself is a low risk class for immunogenicity, the proinflammatory environment may facilitate the induction of anti-drug antibodies. However, current phase 2 clinical study data suggest low rates of immunogenicity to the product (<5%) in patients with SCD. (b) (4)

Given the breakthrough nature of the product, with the accelerated approval schedule, this is acceptable.

2.2 Validation of Anti-Drug Antibody Assay

The original developer (Reprixys Pharmaceuticals) product code for crizanlizumab was SelG1, while the Novartis product code for crizanlizumab is SEG101. These two codes are used in section below in the context of the individual company's ADA assays. Reprixys used a single tiered qualitative AlphaLISA assay developed by (b) (4) to detect the anti-SelG1 in the serum samples from clinical studies A2101(PK/PD in healthy volunteers) or A2201 (efficacy/safety in patients with SCD). No titrating, or neutralizing antibody assays were developed. This assay was discontinued and although Novartis owns the immunogenicity data obtained using this assay, they do not have access to the assay itself, and no further experimental validation is possible at this time without performing a new validation exercise. According to Novartis, samples from clinical studies are also in very limited supply, so they were never retested using the Novartis/(b) (4) developed ADA assays.

Novartis, however, used a tiered approach for ADA testing including screening, confirmatory, and titrating assays to detect anti-SEG1 binding antibodies in the serum samples from clinical studies CSEG101A2102 (PK/PD in Healthy volunteers) or CSEG101A2202 (SCD). A neutralizing antibody (NAb) assay is currently under development and thus was not used to test any clinical study samples but will be used to test confirmed ADA+ study samples in past phase 1 and 2 studies (b) (4). Novartis contracted the development of a MesoScale Discovery (MSD) platform electrochemiluminescence (ECL) bridging ELISA to (b) (4).

Assessor comment:

The Sponsor's plan to test banked samples using NAb assay after approval is acceptable because the clinical results to date indicate the benefit of the drug outweigh the observed risks from ADA.

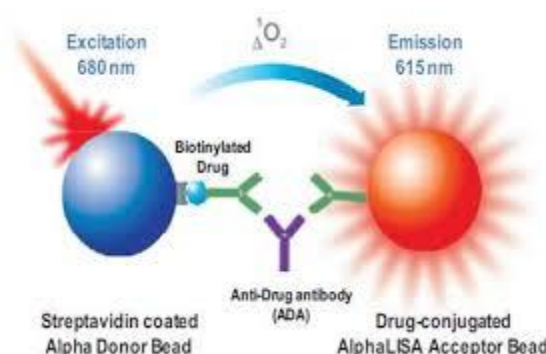
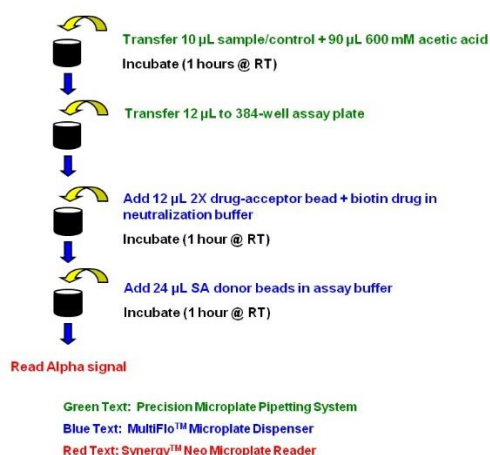
2.2.1 Method Principle

Two types of ADA assays were developed to assess ADA during product development, Reprixys used an Amplified luminescent proximity homogeneous assay (AlphaLISA) platform (b) (4) to test for anti-SelG1 antibodies, while Novartis developed an ECL bridging ELISA (MesoScale Delivery) to test for antiSEG101 antibodies.

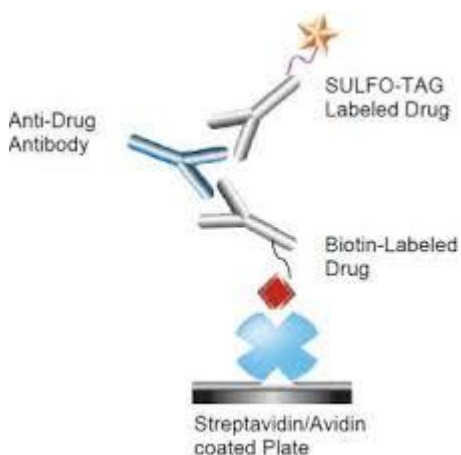
For both sets of screening assays, serum samples are first subjected to treatment with acetic acid to dissociate the pre-formed ADA-drug complexes.

For the Reprixys AlphaLISA, following sample neutralization step, ADAs were captured in solution by a combination of SelG1 acceptor beads (emission at 615nm) and Biotin-SelG1+streptavidin donor beads (excitation 680nm) and incubated onto OptiPlate-96 microplates. After this incubation, the plates are read using the (b) (4) Multilabel Plate Reader and the AlphaLISA relative counts were measured. The higher the level of ADAs present in the sample, the higher the luminescent signal will be in the assay.

AlphaLISA Automated Assay Workflow



For the Novartis MSD ECL bridging ELISA, following the acid neutralization step, samples are then incubated Biotin-SEG101 + Sulfo-Tagged SEG101, and the complexes are added to a streptavidin-coated MesoScale Discovery (MSD) plate. The chemiluminescent signal readout is obtained from an ECL reaction (sTag/ tripropylamine) and measured by an MSD plate reader. The higher the level of ADAs present in the sample, the higher the ECL signal will be in the assay.



If the sample signal is higher than the screening cut-point (SCP), the specificity of the sample for the analyte is confirmed using a confirmatory assay. The confirmatory assay is a competitive inhibition test in which the signal from a sample spiked with an excess amount of SEG101 is compared with the signal from an unspiked sample. Specific ADAs will bind to the spiked SEG101, resulting in a signal reduction compared to the signal from unspiked samples. If the % signal reduction is equal to or greater than the confirmatory cut-point (CCP), the sample is reported as confirmed positive for ADAs.

An ADA titer assay is performed by preparing a dilution series of test samples. The fold dilution of the most diluted sample that exhibits a signal above the SCP is defined as the ADA titer. Titer cut points (TCP) were mathematically derived from resulting dilution curves.

2.2.2 Validation Exercises

Assessor comment: The validation results for ADA assays used in each clinical study and a reviewer assessment are provided in Summary Table 2.1 below. Validation data are not provided unless necessary to discuss any identified issues. The bulk of the assessment was devoted to the ECL MSD bridging ELISA developed by (b) (4) for Novartis, as this is the only is currently active ADA assay used to test samples from Novartis clinical studies A2102, A2202, and A2301 .

Table 2.1: Validation Results and Reviewer Assessment for ADA assays used in Reprixys clinical studies A2101 and A2201 (reports (b) (4) -0066-00/00-(b) (4)) and Novartis Clinical Studies A2102 and A2202 (Validation Reports (b) (4) R1600631-(b) (4))

Abbreviations: ADA: anti-drug antibody; AlphaLISA: Amplified luminescent proximity homogeneous assay; DF: dilution factor; CPF: cut point factor; SCP: screening cut point; CCP: confirmatory cut point; TCP: titer cut point; NC: negative control; PC: positive control; LPC: low positive control; HPC: high positive control; IDC: immunodepletion control; HS: human serum; MSD: mesoscale Delivery; ECL: electrochemiluminescent; NHVS: normal healthy volunteer sera; SCDS: Sickle Cell Disease sera

Validation Parameter	Clin Studies A2101 & A2201 Validation Report: (b) (4) -0066-00/00- (b) (4)	Clin Studies A2102 & A2202 Validation Report: (b) (4) R1600631 (b) (4)	Reviewer Comment
Contract Research Org	(b) (4) Experiments performed by two analysts on three different days.	(b) (4) Experiments performed by two analysts on three different days.	<i>Bioanalytical inspection performed by OSIS at (b) (4). There were no inspectional observations and validation data are reliable.</i>
Assay principle	AlphaLISA: SelG1 coupled to donor/acceptor beads. Luminescence detected only in presence of positive control antisera or sample ADA. The higher the level of ADAs present in the sample, the higher the luminescent signal will be in the assay	MSD-based ECL assay: biotin-SEG101 and sTag-SEG101 onto SA coated MSD plates. ECL signal detected in presence of presence of positive control antisera or sample ADA. The higher the ADA the higher the ECL signal (Relative Light Units) detected Blocking is performed with SuperBlock buffer.	<i>Each ADA Assay use different chemiluminescent reagents. Novartis</i> (b) (4)
Sample Pretreatment (Acid dissociation)	samples diluted 1 in 10 in 600mM Acetic Acid then neutralized 1:1 with SelG1 neutralization buffer	samples diluted 1 in 25 in 300mM Acetic Acid then neutralized 1:1 with neutralization buffer or SEG101 neutralization buffer	<i>Acid dissociation is a common approach to reduce drug interference. A single round of acid dissociation was performed in both assays.</i>
Positive control (PC)	Anti-SelG1 rabbit polyclonal antibody	Anti-SEG101 Polyclonal rabbit Antibody IgG (Lot PR170510C; concentration: 1.84 mg/mL).	<i>Each assay platform used different in-house controls. Controls were appropriately qualified.</i>
PC Dose Curve and Hook Effect	Not Done	0 0.49, 0.98, 1.95, 3.91, 7.81, 15.62, 31.25, 62.5, 250, 500, 1000, 40,000 ng/ml No Hook effect observed	<i>MSD assay: Dose Range is sufficient to establish 4 PL curve fits.</i> <i>No hook effect for NHV sera. No data were provided for SCD sera, but selectivity data suggest that the assay</i>

			<i>performs similarly with SCD sera as with NHV sera.</i>
LPC	2E5 DF LPC $\leq 1/2X$ signal of HPC	10 ng/mL of PC in 100% human serum LPC was based on sensitivity determination and was confirmed by spiking 20 NHV sera.	<i>MSD Assay: LPC concentration acceptable, despite not being statistically set to fail 1% of the time. Original LPC was 50ng/ml but was subsequently adjusted downwards to be closer to limit of detection of assay.</i>
HPC	1E5 DF HPC $> 2X$ signal of LPC	40 ug/mL of PC in 100% HS	<i>MSD Assay: HPC concentration acceptable</i>
IDC	Not Done	50ng/ml PC in 100%HS + 46 ug/ml SEG101	<i>MSD Assay: Demonstrate that signal is below cut point when original LPC is spiked with DP.</i>
Matrix and NC	Normal human (NH) serum pool	Normal human serum pool	<i>The signals of blank samples must be below SCP. The use of healthy human serum pool as the matrix control is acceptable. Selectivity data suggests that SCD pool is not necessary.</i>
MRD	1:100	1:50	<i>Both AlphaLISA and MSD Assays correctly include acid dissociation and buffer neutralization steps to determine MRD.</i>
NC system suitability range	Not provided	Expected response of ≤ 125 ECL	<i>Acceptable for MesoScale Discovery ECL assays</i>
LPC system suitability range	signal/background (S/B) ratios of ≥ 3	Expected response of ≥ 240 and ≤ 323 ECL	<i>Acceptable for MesoScale Discovery ECL assays</i>
HPC system suitability range	signal/background (S/B) ratios of ≥ 3	Expected response of $\geq 580,000$ and $\leq 900,000$ ECL	<i>Acceptable for MesoScale Discovery ECL assays</i>
Screening cut- point (SCP) Floating CP: Mean NC response $\times$ normalization factor	Qualification report unclear how SCP was determined except that it was based on S/B ratios .	SCPF=1.07 from 68 commercial NHVS Sera Used non-parametric 95 th percentile (%5FP)	<i>MSD assay used NHVS to set initial SCPF. Novartis was requested in Aug 20/2019 IR to provide data showing that</i>

	Novartis re-evaluated assay cut point using S/B using pre-dose samples for each clinical study using 99 th percentile (see additional assessor comments)	NHVS FP rate ~2.9%. (6/204) SCPF 1.07 from 55 pre-study baseline SCDS Used non-parametric 95 th percentile (%5FP) SCDS FP rate ~9.09%. (5/55) provided in amend 35	<i>calculated CPF was applicable to SCD sera. In amends 27 and 35, Novartis provided data from 55 SCDS pre-study baseline samples that show similar SCP. FP rate for both populations fell 2-11% after outlier exclusion. Cutpoint assessment is acceptable.</i>
Confirmatory cut-point (CCP) Floating	Assay initially used only SCP; Novartis re-evaluated assay cut point using S/B using pre-dose samples for each clinical study using 99 th percentile.	<i>CCP ≥ 52.3% (based on 68 HVS spiked with LPC; 98% CI; 2%FP). Novartis used conservative 2% FP rather than recommended 1% FP rate.</i>	<i>MSD assay used HVS to set initial CCPF. As SCD sera data submitted in amends 27 and 35 demonstrated that original SCP was suitable for use with both populations, no CCP verification was requested for SCD sera.</i>
Titer Cut Point (TCP)	Titration not performed; Assay can detect baseline positive and treatment-emergent ADAs, but not treatment-boosted ² ADAs	1.12 (99.9% CI, 0.1% FP) Parametrically estimated from PC dose curve (mean ECL+3.09SD)	<i>MSD Assay: The TCP was set appropriately.</i> <i>AlphaLISA assay: titration was not performed.</i>
Assay Drug tolerance	Not Provided	Tested 100 and 250 ng/ml PC against 10, 50, 100, 150, 200, and 250ng/ml SEG101 100 ng/ml of PC tolerant to 82 ug/ml SEG101	<i>Novartis study 2202: Max Drug Ctrough <10 ug/ml for SCD population. MSD assay Drug tolerance is acceptable.</i> <i>Reprixys study 2201: Max Drug Ctrough <15 ug/ml for SCD population.</i>
Sensitivity	Not Provided	10ng/ml;	<i>MSD assay sensitivity acceptable</i>
Repeatability/Intra-assay variability	Not Provided	NC %CV 2.5-5.8 LPC %CV 1.2-5.3 HPC %CV 1.0-19.5	<i>Repeatability for MSD assay <20% and is acceptable</i>
Intermediate Precision (IP)/inter-assay variability	Not Provided	NC %CV 13.7 LPC %CV 18.2 HPC %CV 20.7	<i>MSD assay IP for PCs<21% and is acceptable.</i>
Selectivity/Specificity	Performed only specificity: Anti-SelG1 rabbit PC, Rabbit IgG NC ≤ 30% PC	20/20 HV sera and 6/6 SCD sera spiked with LPC and HPC all	<i>MSD assay: selectivity suitably demonstrated with both HVS and SCD</i>

² Treatment boosted- Baseline ADA positive subjects that show in a ≥2-fold titer increases following treatment.

	Human IgG NC $\leq$ 20% PC	screened and confirmed positive (100%) and negative without spike	<i>sera suggesting matrix effects are minimal.</i>
Stability	Not Done	LPC and HPC 6F/T - 20°C to RT cycles 48h at RT	<i>MSD Assay: Stability testing shows PC remain stable for up to 6 freeze thaw cycles when stored at $\leq$ -20°C, and up to 48hrs at RT. This is acceptable.</i>
Lipemia	Not Done	3 lipemic HV sera shown not to impact LPC detection	<i>MSD Assay: Data indicate lipemia does not impact ADA assay. Testing is acceptable</i>
Hemolysis	Not Done	3 hemolyzed HV sera shown not to impact LPC detection. No data provided with SCD sera,	<i>MSD Assay: Data indicate hemolysis does not impact ADA assay. Although SJD sera may be more prone to hemolysis, and no data was provided for SCD sera, selectivity data suggest that clinical population matrix is unlikely to impact assay.</i>
Robustness	Not done	Summarized testing performed during development: different batches of SEG101, biotin SEG101, sTag-SEG101, anti-SEG101 PC, and SSC pooled matrix/NC	<i>MSD Assay: based on provided summary, robustness testing appears acceptable.</i>
ADA Assay Assessment	Assay was qualified for use with monkey and human serum, and full validation was never completed. Assay qualification report is included in Module 4 rather than Module 5. Based on my assessment of the report provided, assay is not validated, and immunogenicity data from two Reprixys studies should be viewed as interim data.	Assay determined to be suitable for intended purpose post-amendments 27 and 35.	MSD assay: assay is suitable for testing NHVS samples and SCDS samples. AlphaLISA: assay not validated.

Additional Reviewer Comments:

The original Reprixys AlphaLISA method that was used to test samples from clinical studies A2101 and A2201 for ADAs was never fully validated and is currently inactive. Novartis opted to develop a new set of assays based on MSD platform instead of using the Reprixys AlphaLISA ADA method. However, so as to be able to utilize the immunogenicity data from Reprixys, Novartis re-evaluated the screening assay cut-point for each clinical study using predose sample values, by normalizing against negative control of each plate (S/N ratios), performing an outlier analysis which excluded samples above 75th percentile+1.5 (75th percentile–25th percentile) or below 25th percentile–1.5 (75th percentile–25th percentile), and calculating 99th percentile of the remaining values as the new study specific cut point. Based on requested tabular summary data provided in amend 10 (7/10/2019)

(b) (4)

2.3 Validation of Neutralizing Antibody Assay

Assessor comment: Novartis did not submit NAb assay validation report in SN01. In their IR response submitted under SN10 (07/10/ 2019) Novartis revealed that NAb assay is currently under development and will be used to test ADA+ samples from completed clinical studies A2102, A2202, (b) (4) Reprixys never developed a NAb assay for SelG1.

2.3.1 Method Principle

According to SN10 (07/10/2019, the Nab assay under development is based on a SPEAD approach (Solid Phase Extraction with Acid Dissociation) followed by an MSD-based competitive ligand binding assay. Samples are incubated with biotin-SEG101 to form nAb/drug complexes. These samples are immobilized on to a SA coated plate. Following incubation and subsequent acid-dissociation to release antibodies, the samples are then transferred and neutralized on a second biotin-SEG101 coated SA-MSD plate and incubated. For detection, the subsequent addition of s-Tag P-selectin, which binds to any fixed biotin-SEG101, allowing any unbound material to be washed away. Read buffer is added and the s-Tag associated with labelled drug produces a chemiluminescent signal when an electrical voltage is applied. Presence of neutralizing antibody bound to biotin SEG101 would not allow for s-Tag P-selectin-biotin crizanlizumab complex to form therefore leading to a reduction of signal in the presence nAb.

Additional Reviewer Comments:

The lack of NAb assay is not an approvability issue but will necessitate a PMC. Based on discussion

held during midcycle communication (Aug 27, 2019) Novartis plans to submit the NAb assay validation post-approval when they submit efficacy supplement with their results from Phase 3 clinical study A2301.

2.4 Facility Inspection Summary

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) performed a bioanalytical inspection between [REDACTED] (b) (4) [REDACTED] the CRO responsible for developing immunogenicity assays and performing clinical sample analysis for Novartis under BLA 761128. There were no inspectional items raised by OSIS inspector [REDACTED] (b) (4) and bioanalytical data reported to the agency is considered reliable to support a regulatory decision.

2.5 Assessment of Assay performance in Clinical Studies

2.5.1 Executive Summary

Table below summarizes clinical studies with immunogenicity component along with resulting ADA results. For detailed analysis on impact of ADA on efficacy and safety refer to the Clinical and Clinical Pharm reviews

Study #	Sponsor	• Study details	Assessor Comments
(b) (4)			
Study A2201 (Pivotal Study)		• Efficacy, safety, PK/PD of SelG1, SCD Patients, N=198 • Multiple doses of 2.5 mg/kg, 5 mg/kg and placebo using SelG1 product	• ADA assay: AlphaLISA not validated • ADA rates post Novartis cutpoint reassessment 10/137 (7.1%) SCD sera • 2/10 treatment-emergent • 8/10 positive at baseline, d15, week 14-26 • No apparent impact on PK/PD or AE • ADA rates based on summary immunogenicity data tables provided in SN10 (7/10/19)
Study A2102 (PK Comparability)	Novartis	• PK/PD comparability of SelG1 vs. SEG101, safety, HS, N=68 • Single dose of 5 mg/kg (N=61) and 7.5 mg/kg (N=7)	• ADA assay: MSD bridging ELISA validated • ADA rates 2/67 (2.99%) healthy subject sera • No apparent impact on PK/PD or AE • ADA rates based on summary immunogenicity data tables provided in SN10 (7/10/19)

Study A2202 IA (PK/PD)		• PK/PD, safety, SCD Patients, N=45 • Multiple doses of 5 mg/kg and 7.5 mg/kg (N=10) using SEG101 product	• ADA assay: MSD bridging ELISA validated • ADA rates 0/44 (0%) SCD sera • Study is ongoing. ADA rates based on summary immunogenicity data tables provided in SN10 (7/10/19)
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Assessor comment: *Crizanlizumab has breakthrough designation and an accelerated approval pathway. Therefore, limited immunogenicity data derived from two phase 1 (A2101 and A2102) and two phase 2 clinical studies (A2201 and A2202) are reported in this submission of BLA 761128. The value of the available data is further impacted by the use of two different sets of immunogenicity assays- Reprixys AlphaLISA (A2101 and A2201) and Novartis' MSD bridging ELISA (A2102 and A2202). Of these two set of assays, only the MSD ELISA was fully validated. Thus, only immunogenicity data obtained using the validated MSD bridging ELISA should be used to support immunogenicity label in section 6.2. The limited immunogenicity data is not an approvability issue because the safety and efficacy profile support approval. A Phase 3 Efficacy study, CSEG101 A2301, is currently ongoing and will provide additional efficacy, safety and immunogenicity data. Novartis will use the recommended tiered approach of screening, confirmatory, titering and neutralizing antibody assays to analyze resulting immunogenicity data.* (b) (4)

The text proposed for section 6.2 of the label is provided below:

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. (b) (4)

Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies (b) (4)

(b) (4)

Assessor comment: (b) (4)



Joao
Pedras
Vasconcel

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Susan
Kirshner

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Date: 10/23/2019 09:25:33AM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
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To: Administrative File, STN 761128/0
From: Diane Raccasi, Reviewer, CDER/OPQ/OPF/DMA/Branch IV
Through: Reyes Candau-Chacon, Ph.D. Quality Assessment Lead, CDER/OPQ/OPF/DMA/Branch IV
Subject: New Biologic License Application (BLA)
US License: 0021
Applicant: Novartis Pharmaceuticals Corporation
Facilities: Novartis Pharma, Stein AG, CH-4332 Stein, Switzerland (FEI 3002653483)
Product: Crizanlizumab
Dosage: 10mg/mL solution for intravenous infusion
Indication: Sick cell disease
Due date: November 16, 2019 (primary review due date October 16, 2019)

Recommendation for Approvability: The drug product section of BLA 761128 is recommended for approval from a sterility assurance and microbiology product quality perspective with the following pot-marketing commitment:

“To develop an endotoxin detection method capable of detecting endotoxin from the DP release samples”

Review Summary

Novartis submitted BLA 761128 to license the Crizanlizumab and the manufacturing process. This review contains the microbiology drug product quality assessment for the manufacturing process of Crizanlizumab drug product. All other aspects of the submission are deferred to OBP. BLA 761128 was submitted in eCTD on May 16, 2019 in electronic format under sequence 0004.

Drug Product Quality Microbiology Information Reviewed

Description	eCTD	Date
Original BLA	0004	May 16, 2019
Amendment	0012	August 7, 2019
Amendment	0023	August 21, 2019
Amendment	0028	September 4, 2019
Amendment	0032	September 13, 2019
Amendment	0041	October 22, 2019
Amendment	0042	October 24, 2019

DMF	Content	Date Reviewed	Finding	Reviewed by
	(b) (4)			
		3/28/2019	Adequate	Yuansha Chen

Module 1

1.14 Labeling

The instructions for use include Crizanlizumab (SEG101) at 5 mg/kg administered over a period of 30 minutes by intravenous infusion at week 0, week 2 and every 4 weeks thereafter. The instruction for preparation requires calculation of the Crizanlizumab administration volume which is diluted in 0.9% sodium chloride or 5% dextrose to a total volume of 100mL for IV infusion. The product is stored and transported at 2-8°C. The diluted solution for infusion should be prepared by a health care provided using aseptic technique. Once the diluted solution for infusion is prepared it should be administered as soon as possible; however, the prepared solution can be stored at 25°C for (b) (4) 4.5 hours from start of preparation to completion of infusion or under refrigerated conditions at 2-8°C for (b) (4) 24 hours from the start of preparation to the completion of infusion.

Reviewer comments: The sponsor did not provide data to support the post-dilution refrigerated storage conditions at 2-8°C for ≤ 24 hours stated in the label.

Reviewer's question: IR#1 (eCTD 0012) 7/10/2019 requested the sponsor to provide the microbiological study to support the labeled storage conditions. The request included a description of the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions and be conducted for twice the recommended storage period. In lieu of this data, update the label to reduce the post-dilution storage period to not more than 4 hours.

Response summary: The sponsor stated a study was conducted with the lowest and highest dilutions using USP required organisms plus *Enterococcus faecium* (ATCC 6057) to demonstrate an environmental isolate at 2-8°C for 48 hours. Crizanlizumab product testing included 1.0 mg/mL in 0.9% saline, 9.6 mg/mL in 0.9% saline, 1.0 mg/mL in 5% dextrose, and 9.6 mg/mL in 5% dextrose. Samples were pulled at 0, 12, 24, and 48 hours. Microbial inoculum included <100 CFU/mL with a volume not to exceed 1% of the test diluted solution. The results provided in a line chart indicate that microbial increase was $\leq 5 \log_{10}$ over the 48-hour period.

Reviewer comments: The sponsor did not provide data to support the post-dilution study. The results were provided in a line chart with the y-axis increments of 1, 10 and 100 CFU/mL(log). Based on the size of the chart and the large increments of the y-axis it is not possible to determine the CFU/mL values recovered at the 0, 12, 24 and 48 timepoints.

Reviewer's question: IR#2 (eCTD 0023) 8/21/2019 requesting the sponsor to provide the microbiological data supporting post-dilution storage conditions included in the label (24 hours at 2 to 8 °C) are provided in Figures 3-1, 3-2, 3-3 and 3-4. Provide the microbiological data associated with Figures 3-1, 3-2, 3-3 and 3-4 in tabular format to facilitate an assessment of the provided data.

Response summary: The sponsor's response included raw data associated with the 2-8°C 48 hour hold time study. The recovery method was validated to be within 50-200% of the inoculum and the time zero sample was pulled after a 1.5-hour incubation at room temperature to simulate the infusion preparation time. The raw data associated with the post-dilution hold time study is provided in Tables 7-1, 7-2, 7-3 and 7-4 of the response and is reconstructed below.

	1.0mg/mL in 0.9% saline				9.6%mg/mL in 0.9% saline			
Incubation hours	0	12	24	48	0	12	24	48
<i>Aspergillus brasiliensis</i>	21	25	29	26	37	30	34	24
<i>Candida albicans</i>	80	80	69	70	76	82	77	41
<i>Escherichia coli</i>	40	46	48	50	40	42	42	33
<i>Staphylococcus aureus</i>	43	54	51	54	42	36	38	32
<i>Pseudomonas aeruginosa</i>	11	14	8	10	1	0	1	0
<i>Staphylococcus epidermidis</i>	59	56	48	45	51	58	43	41
<i>Enterococcus faecium</i>	54	59	44	44	44	47	41	46

	1.0mg/mL in 0.5% dextrose				9.6%mg/mL in 0.5% dextrose			
Incubation hours	0	12	24	48	0	12	24	48
<i>Aspergillus brasiliensis</i>	25	28	31	20	36	43	47	24
<i>Candida albicans</i>	73	77	64	61	75	87	75	42
<i>Escherichia coli</i>	44	30	36	32	32	31	41	43
<i>Staphylococcus aureus</i>	43	44	30	31	38	43	32	37
<i>Pseudomonas aeruginosa</i>	9	7	7	5	0	0	0	1
<i>Staphylococcus epidermidis</i>	50	54	48	43	53	50	49	49
<i>Enterococcus faecium</i>	49	44	40	40	54	59	43	51

Reviewer comments: The data includes up to a 48-hour incubation which is satisfactory for the 24-hour storage condition at 2-8°C. The data demonstrates the solutions are not growth promoting for the time and temperature tested indicating the 24-hour storage time is acceptable.

Satisfactory

P.1 Description and Composition of the Drug Product

Crizanlizumab is a selective IgG2 kappa humanized monoclonal antibody that binds to P-selectin which in a chronic pro-inflammatory state is over-expressed and is an adhesion molecule on endothelial cells and platelets. P-selecting multi-cellular adhesion is a key factor in the pathogenesis of vaso-occlusion and vaso-occlusive crisis (VOC). VOC induces severe pain, and results in increased morbidity, decreased quality of life, and can result in organ damage/failure, stroke and/or death.

The drug product is a sterile, single use, preservative-free, colorless to slightly brownish yellow (b) (4) for solution for infusion.

Composition

The composition of the DP is reconstructed below from Table 2-1 provided in the submission.

Ingredient	Amount	Function	Reference Standard
Crizanlizumab	100.0 mg	Active ingredient	Novartis monograph
Sucrose	753.3 mg	(b) (4)	Ph. Eur: USP/NF
Sodium citrate	50.53 mg		
Citric acid	5.40 mg		
Polysorbate 80	2.00 mg		
WFI	(b) (4)		

Container and closure

The container closure system includes colorless Type I glass with a grey rubber stopper sealed with an aluminum cap and a yellow plastic flip-off disk.

The description is satisfactory

P.2 Pharmaceutical Development; Control Strategy

(b) (4)

P.3 Manufacture**P.2.1 Manufacturer(s)**

The manufacture, quality control, stability testing and packaging of Crizanlizumab (SEG101) (b) (4) is performed at the following facilities as described in Table 1-1 of the submission:

Activity	Name	Address
Manufacturing	Novartis	Stein AG, Schaffhauserstrasse, CH-4332 Stein, Switzerland (FEI 3002653483)
Quality Control		
Storage		
Stability testing		
Secondary Packaging		
Secondary Packaging		

(b) (4)

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Conclusion

- I. The Drug Product section of this BLA, as amended, was reviewed from a sterility assurance and microbiology product quality perspective and it is recommended for approval with the following post-marketing commitment provided by the sponsor:

To develop an endotoxin detection method capable of detecting endotoxin from the DP release samples.
- II. Information and data in this submission not related to sterility assurance of the drug product should be reviewed by the appropriate division.
- III. Refer to Panorama for the cGMP status of the manufacturing facility.



Reyes
Candau-Chacon

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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Memorandum of Review to the File

Submission Tracking

Number: 761128/0
Subject: New Biologics License Application
Review/Revision Date: 10/02/2019
Primary Reviewer: Maxwell Van Tassell, Ph.D., Microbiologist
Secondary Reviewer: Reyes Candau-Chacon, Ph.D., Quality Assessment Lead
Applicant: Novartis Pharmaceuticals Corporation
US License Number: 0021
Product: Adakveo (crizanlizumab)
DS Manufacturing Site: Novartis Pharma AG, Basel, Switzerland (FEI: 3002807772)
Indication: Sick cell disease
Dosage Form: (b) (4) solution for IV infusion, 10 mg/mL
FDA Receipt Date: 05/16/2019
Action Date: 01/16/2020

Recommendation for Approvability: (STN) 761128/0 was reviewed from a product quality microbiology perspective and is recommended for approval.

PRODUCT QUALITY MICROBIOLOGY ASSESSMENT: DRUG SUBSTANCE

Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
eCTD 0004	05/16/2019	Rolling BLA Submission including Module 3
eCTD 0029	09/06/2019	Response to Information Request
eCTD 0037	09/26/2019	Response to Information Request

MODULE 3.2.S DRUG SUBSTANCE

S.1 GENERAL INFORMATION

Crizanlizumab is a humanized anti-human-P-selectin monoclonal antibody expressed in CHO-(b) (4) cells.

THE DESCRIPTION IS SATISFACTORY



Maxwell
Van Tassell

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Reyes
Candau-Chacon

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